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193

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of:) Group Art Unit: 1804
)
Gjerset and Sobol) Examiner: Low, C.
)
Serial No.: 08/335,461)
)
Filed: November 7, 1994)
)
For: ENHANCING THE SENSITIVITY)
OF TUMOR CELLS TO THERAPIES)

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APPELLANT'S BRIEF ON APPEAL
SUBMITTED PURSUANT TO 37 C.F.R. § 1.192

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Applicant hereby appeals the Examiner's final rejection
mailed June 24, 1996 and responds to the Notification of Non-

CERTIFICATE OF MAILING

I hereby certify that this paper (along with any referred to as being attached or enclosed) is being deposited with the United States Postal Service on the date shown below with sufficient postage as Express Mail in an envelope addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

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May 30, 1997

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Kelly Glass

name of person mailing paper

signature of person mailing paper

210/048
Patent

Compliance With 37 C.F.R. 1.192(c) mailed May 19, 1997. A
Request for Oral Hearing, a Petition for Automatic Extension, and
fees in the amount of \$1,015.00 as required under 37 C.F.R. §
1.17(d), 1.17(f), 1.17(g), and 1.192(a) were filed on April 24,
1997. If any additional fees are required with this filing,
please charge our Deposit Account No. 12-2475 for the appropriate
amount.

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35 U.S.C. § 112 1,3,6,11,13,14

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MISCELLANEOUS

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REAL PARTY IN INTEREST

SIDNEY KIMMEL CANCER CENTER is the assignee of the above captioned patent application.

INTROGEN THERAPEUTIC, INC. is the sole existing licensee of the above captioned patent application.

RELATED APPEALS AND INTERFERENCES

Neither Appellant nor Appellant's legal representative or assignee is aware of any appeals or interferences which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

STATUS OF THE CLAIMS

Claims 1, 2, 4-20 and 23 are pending (see Appendix).

All pending claims are rejected under 35 U.S.C. § 112, first paragraph, as the specification allegedly does not contain a written description of the claimed invention.

All pending claims are rejected under 35 U.S.C. § 112, second paragraph, as allegedly failing to particularly point out and distinctly claim the subject matter which applicant regards

as the invention.

All pending claims are rejected under 35 U.S.C.
§ 103(a) as allegedly being unpatentable over Cheng et al.,
Srivastava, Moossa et al., Wu et al., Malkin et al., Chen et al.,
Nabel et al., Itoh et al. and Eppstein et al.

STATUS OF AMENDMENTS

Claims 3, 21 and 22 have been canceled without
prejudice to further prosecution thereof. Amendments to claims
1, 2, 6, 9, 10, 12-15, 17-20 and 23 were filed after the Final
Office Action. These amendments were made to narrow issues for
appeal and to adopt the Examiner's suggestions in the Final
Office Action. Applicant submits that the amendments do not
necessitate a new search or raise any issue of new matter. The
Examiner has indicated in an Advisory Action mailed March 11,
1997 that the proposed amendments will be entered upon the filing
of an Appeal Brief.

SUMMARY OF THE INVENTION

The present invention relates to a process of enhancing

the therapeutic effect of a cancer therapy such as chemotherapy or radiation therapy.

It has been known in the art that many types of human cancer cells carry mutations in the p53 gene. Some prior art references have shown that the introduction of a wild-type p53 gene into a variety of cancer cells reduces their growth rate. p53 gene is therefore known as a tumor suppressor gene.

Within the scope of this invention, Applicant has discovered a new function of the wild type p53 gene, namely, its ability to increase the sensitivity of a tumor cell lacking an endogenous wild-type p53 gene to cancer therapies. Therefore, the introduction of a wild-type p53 gene or protein into a tumor cell deficient in its wild-type p53 gene may be combined with a conventional cancer therapy to increase the therapeutic effect of the conventional cancer therapy, i.e., to kill cancer cells and/or to suppress tumor growth.

In that regard, this invention features a process of increasing the therapeutic effect of a cancer therapy by introducing a wild-type p53 gene into a tumor cell lacking an endogenous wild-type p53 gene and expressing the heterologous

wild-type p53 gene before subjecting the tumor cell to the cancer therapy.

Cancer therapies which can be augmented by this process include radiation therapy, chemotherapy, immunotherapy, cryotherapy and hyperthermia. Tumors which can be treated by this process include leukemia, lymphoma, ovarian carcinoma, osteogenic sarcoma, lung carcinoma, colorectal carcinoma, hepatocellular carcinoma, glioblastoma, prostate cancer, breast cancer, bladder cancer, kidney cancer, pancreatic cancer, gastric cancer, esophageal cancer, anal cancer, biliary cancer, and urogenital cancer.

In a preferred embodiment, the wild-type p53 gene is included in a vector such as adenovirus vector, retroviral vector, adeno-associated virus vector, herpes virus vector, vaccinia virus vector and papilloma virus vector.

In other preferred embodiments, the wild-type p53 gene is coupled to a virus capsid or particle, encapsulated in a liposome, or conjugated with a ligand such as an asialoglycoprotein. The wild-type p53 gene may be introduced to the tumor cell with an aerosolized preparation or by direct

injection, intra-arterial infusion, intravenous infusion, or intracavitary infusion.

Alternatively, a wild-type p53 protein is introduced into the tumor cell in place of the wild-type p53 gene.

ISSUES

(a) Whether pending claims 1, 2, 4-20 and 23 are supported by a written description in the original specification whereas these claims are of similar scope and wordings with the original claims?

(b) Whether claims 1, 2, 4-20 and 23 clearly and precisely define the invention whereas terms and phrases well known to those skilled in the art are used?

(c) Whether the invention of claims 1, 2, 4-20 and 23 is obvious in view of the nine references cited by the Examiner whereas these references only motivate one skilled in the art to use a wild-type p53 gene to suppress tumor growth but teach away from using the gene to sensitize tumor cells to cancer therapies?

GROUPING OF CLAIMS

Pending claims 1, 2, 4-20 and 23 will be considered in one group.

ARGUMENT

I. THE SPECIFICATION CLEARLY DESCRIBES THE INVENTION OF CLAIMS 1, 2, 4-20 AND 23

In the Final Office Action mailed June 24, 1996, the Examiner acknowledged the utility of the claimed invention but rejected the pending claims for inadequate written description, stating on page 11 of the Final Office Action that "[t]he rejection is not one for lack of utility but for inadequate written description of the invention."

The Examiner also stated on page 2 of the Final Office Action:

Claims 1-23 are rejected under 35 U.S.C. 112, first paragraph, as the specification does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed.

Applicant respectfully traverses this rejection.

- A. Claims 1, 2, 4-20 and 23 define an invention that is clearly conveyed to those skilled in the art at the time the application was filed

The invention claimed in claims 1, 4-20 and 23 features a process of increasing the therapeutic effect of a cancer therapy by introducing a wild-type p53 gene into a tumor cell lacking an endogenous wild-type p53 gene. This process expresses the heterologous wild-type p53 gene in the tumor cell before subjecting the tumor cell to the cancer therapy. Claim 2 substitutes the wild-type p53 gene with a wild-type p53 protein.

"A written description requirement issue generally involves the question of whether the subject matter of a claim is supported by the disclosure of an application as filed." MPEP § 2163.01. "Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed." MPEP § 2163.02.

Applying the factual inquiry to this case, one skilled in the art would find that claims 1, 2, 4-20 and 23 are described in both the original claims and the original specification of this application.

For example, the original claims 1 and 22 state:

(1) Method of increasing the effect of a cancer therapy, comprising the steps of:

delivering wild-type therapy-sensitizing gene activity to a tumor cell characterized by loss of said wild-type therapy-sensitizing gene activity, and

subjecting said tumor cell to said cancer therapy.

(22) The method of claim 1, wherein said therapy-sensitizing gene activity is p53 therapy-sensitizing activity.

Original claims constitute their own description, and later added claims of similar scope and wording are described thereby. In re Koller, 204 U.S.P.Q. 702, 706 (CCPA 1980).

Pending claims 1 and 2 are of similar scope and wording to the original claim 22. The only difference between pending claims 1 and 2 and the original claim 22 is that the claim scope has been narrowed from the "p53 therapy-sensitizing activity" to the "wild-type p53 gene" in claim 1 and the "wild-type p53 protein" in claim 2. In that regard, the original specification explains that the p53 therapy-sensitizing activity is embodied in the wild-type p53 gene and the wild-type p53 protein.

The original specification on pages 13-16 illustrates a general procedure for carrying out the method for enhancing the

effect of a cancer therapy with a wild-type p53 gene or protein. In addition, Example 1 of the specification describes introducing a wild-type p53 gene into a tumor cell. Example 2 of the specification describes introducing a wild-type p53 protein into a tumor cell.

In Example 4, a plasmid containing a wild-type p53 gene was transfected into glioblastoma cells which do not contain endogenous wild-type p53 gene. The wild-type p53 gene was expressed in these cells before these cells were treated with a chemotherapy drug, cisplatin. It was described in the specification that the tumor cells with the transfected wild-type p53 gene were considerably more sensitive to the chemotherapy drug than those not having the wild-type p53 gene.

In Example 5, the cells described in Example 4 were subject to gamma radiation. It was described in the specification that the tumor cells with the transfected wild-type p53 gene were considerably more sensitive to the radiation therapy than those not having the wild-type p53 gene.

In addition, pending claims 4-20 are of similar scope and wording to the original claims 4-20. Pending claim 23 is of

similar scope and wording to the original claim 17.

Accordingly, Applicant submits that one skilled in the art reading the original claims and the original disclosure would recognize that the inventors had possession at the filing of this application the invention covered by the pending claims 1, 2, 4-20 and 23.

B. The Examiner has failed to carry the burden of proof

The examiner has the initial burden of presenting evidence or reasons why persons skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims. In re Wertheim, 191 U.S.P.Q. 90, 98 (CCPA 1976); Ex parte Sorensen, 3 U.S.P.Q.2d 1462, 1463 (Bd. Pat. App. & Inter. 1987).

* * *

Any time an examiner bases a rejection of a claim . . . on the lack of a written description, the examiner should:

- (1) identify the claim limitation not described;
and
- (2) provide reasons why persons skilled in the art at the time the application was filed would not have recognized the description of this limitation in the disclosure of the application as filed.

MPEP § 2163.04.

In the Final Office Action, however, the Examiner did not identify any claim limitation in any of claims 1-23 which is

not described in the original specification or the original claims. Neither did the Examiner explain why those skilled in the art would not have recognized any claim limitation in any of claims 1-23 in the original specification or the original claims.

For the above stated reasons, Applicant submits that pending claims 1, 2, 4-20 and 23 are clearly and fully described in the specification.

II. CLAIMS 1, 2 AND 9 CLEARLY AND PRECISELY DEFINE THE INVENTION TO THOSE SKILLED IN THE ART

In an Advisory Action mailed March 11, 1997, the Examiner repeated his rejection against claims 1, 2 and 9 under 35 U.S.C. § 112, second paragraph.

According to the Examiner, claim 1 is indefinite because the claim does not give definite answers to the following five questions:

- (1) What is the therapeutic effect of a cancer therapy?
- (2) What effect does the wild-type p53 gene accomplish?
- (3) Whether lethal doses of the cancer therapy is included or excluded?
- (4) What is the wild-type p53 gene?

(5) How is the wild-type p53 gene delivered?

The Examiner also stated that claim 2 is indefinite because the claim does not indicate what DNA is or is not the "wild-type p53 gene." In addition, the Examiner stated that claim 9 is indefinite because it is not clear how the different types of cancer cells listed in claim 9 differ from each other.

Applicant respectfully traverses this rejection.

A. The terms and phrases used in claims 1, 2 and 9 have well defined meanings to those skilled in the art

According to MPEP § 2173.02:

Definiteness of claim language must be analyzed, not in a vacuum, but in light of (1) the content of the particular application disclosure, (2) the teachings of the prior art, and (3) the claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made.

In that regard, claim 1 clearly answers the five questions raised by the Examiner when read in light of the specification and the teachings of the prior art.

(1) It is well known to those skilled in the art that the therapeutic effect of a cancer therapy is to kill cancer cells and/or repress tumor growth. A patent need not teach, and

preferably omits, what is well known in the art. Hybritech Inc. v. Monoclonal Antibodies, Inc., 231 U.S.P.Q. 81, 94 (Fed. Cir. 1986).

(2) Claim 1 and the specification made it clear that the effect accomplished by the wild-type p53 gene is to sensitize a cancer cell lacking an endogenous wild-type p53 gene to conventional cancer therapy. How does the wild-type p53 gene accomplish the effect is irrelevant here because "it is axiomatic that an inventor need not comprehend the scientific principles on which the practical effectiveness of his invention rests." Fromson v. Advance Offset Plate, Inc., 219 U.S.P.Q. 1137, 1140 (Fed. Cir. 1983).

(3) As described in the specification, the determination of effective dosage levels of the cancer therapy and the wild-type p53 gene is within the ambit of one skilled in the art. The dosage will vary depending on elements such as the condition of the patient and the cancer being treated. According to MPEP § 2173.04:

Breadth of a claim is not to be equated with indefiniteness. In re Miller, 169 U.S.P.Q. 597 (CCPA 1971). If the scope of the subject matter embraced by the claims is clear, and if applicants have not other

wise indicated that they intend the invention to be of a scope different from that defined in the claims, then the claims comply with 35 U.S.C. § 112, second paragraph.

Because one skilled in the art would know how to adjust the dosage to treat a particular cancer in a particular patient, claim 1 does not become indefinite because a dosage is not specified there.

(4) About half of the cancers have been identified to contain mutated p53 genes since the discovery of p53 gene in the 1980s. As shown by the references cited by the Examiner in the section 103 rejection, those skilled in the art are familiar with what is a wild-type p53 gene and what is a mutated p53 gene. "An inventor need not, however, explain every detail since he is speaking to those skilled in the art. What is conventional knowledge will be read into the disclosure." In re Howarth, 210 U.S.P.Q. 689, 691 (CCPA 1981).

(5) The principle spelled out in In re Howarth applies to the introduction of the wild-type p53 gene into a tumor cell as well. As described in Example 1 of the specification, numerous techniques for delivering a gene into a cell are known to those skilled in the art. It is unnecessary for purposes of

35 U.S.C. § 112, second paragraph, to state in claim 1 a specific method of deliverance because "[n]ot every last detail is to be described, else patent specifications would turn into production specifications, which they were never intended to be." In re Gay, 135 U.S.P.Q. 311, 316 (CCPA 1962).

The Examiner objected to the inclusion of ovarian cancer cells and urogenital cancer cells in the same Markush group. The Examiner also objected to the inclusion of colorectal cancer cells and anal cancer cells in the same Markush group. However, the inclusion of these elements in the same Markush group is permitted by MPEP § 2173.05(h):

The use of Markush claims of diminishing scope should not, in itself, be considered a sufficient basis for objection to or rejection of claims. ... Similarly, the double inclusion of an element by members of a Markush group is not, in itself, sufficient basis for objection to or rejection of claims. ... The mere fact that a compound may be embraced by more than one member of a Markush group recited in the claim does not necessarily render the scope of the claim unclear. For example, the Markush group, "selected from the group consisting of amino, halogen, nitro, chloro and alkyl" should be acceptable even though "halogen" is generic to "chloro."

* * *

it is sufficient if the members of the group are disclosed in the specification to possess at least one property in common which is mainly responsible for their function in the claimed relationship . . .

In this case, the above mentioned cancer cells are included in the same Markush group because they share a common characteristic, i.e., deficiency in their wild-type p53 gene. Therefore, their inclusion in the same Markush group is appropriate even though they overlap with each other.

III. CLAIMS 1, 2, 4-20 AND 23 ARE NOT OBVIOUS IN VIEW OF THE REFERENCES CITED BY THE EXAMINER

The Examiner rejected claims 1-11, 17-20 and 22 under 35 U.S.C. § 103 as allegedly being unpatentable over Cheng et al. taken with Srivastava and Moossa et al. Claims 12-18 and 20 are rejected under 35 U.S.C. § 103 as allegedly being unpatentable over Cheng et al. taken with Srivastava, Moossa et al. and further in view of Wu et al., Malkin et al. and Chen et al. Claims 1-15, 17-20 and 22 are rejected under 35 U.S.C. § 103 as allegedly being unpatentable over Nabel et al. taken with Wu et al., Malkin et al. and Moossa et al. Claim 21 is rejected under 35 U.S.C. § 103 as allegedly being unpatentable over Cheng et al. taken with Srivastava, Moossa et al., or over Nabel et al. taken

with Wu et al., Malkin et al. and Moossa et al., and further in view of Itoh et al. Claim 23 is rejected under 35 U.S.C. § 103 as allegedly being unpatentable over Cheng et al. taken with Srivastava, Moossa et al., or over Nabel et al. taken with Wu et al., Malkin et al. and Moossa et al., and further in view of Eppstein et al.

However, given the differences between the present invention and the references cited by the Examiner, the references fail to support a *prima facie* case of obviousness.

A. The References Cited By The Examiner

Cheng et al. expressed a wild-type p53 gene in the human T leukemia cell line Be-13. The expression of the wild-type p53 gene reduced the growth rate of the leukemia cells, suppressed colony formation of the leukemia cells in methylcellulose cultures, and abrogated the leukemia cells' tumorigenic phenotype in nude mice.

Srivastava described hybrid parvovirus vectors for delivering genes into a cell.

Moossa et al. described conventional cancer therapies

such as radiation therapy, chemotherapy, biological therapy, cryotherapy and hyperthermia.

Wu et al. described a targetable gene delivery system for introducing foreign genes into mammalian cells through receptor-mediated endocytosis.

Malkin et al. described that mutations of the *p53* gene occur not only as somatic mutations in human cancers, but also as germ line mutations in some cancer-prone families.

Chen et al. expressed a wild-type *p53* gene in a peripheral neuroepithelioma cell line (A673). The expression of the wild-type *p53* gene reduced the tumor cells' ability to form colonies in soft agar and tumors in nude mice.

Nabel et al. described delivering proteins to discrete blood vessel segments by catheterization using genetically modified or normal cells or other vector systems.

Itoh et al. isolated cDNA encoding human Fas antigen determinant from human T cell lymphoma KT-3 cells. When they expressed the cDNA in murine T cell lymphoma WR19L or fibroblast L929, the transformed cells were killed by mouse anti-Fas antibody by apoptosis.

Eppstein et al. described liposome formulations which can be used to transport DNA, RNA or polypeptide into cells.

- B. The references cited by the Examiner fail to support a prima facie case of obviousness when all limitations of the claims are considered

When evaluating a claim for determining obviousness, all limitations of the claim must be evaluated. In re Gulack, 217 U.S.P.Q. 401 (Fed. Cir. 1983).

The claimed invention increases the therapeutic effect of a conventional cancer therapy with a process that contains at least two steps:

- (1) deliver a wild-type p53 gene to a tumor cell that has lost its wild-type p53 gene and effect the expression of the wild-type p53 gene; and then
- (2) subject the tumor cell to a conventional cancer therapy such as radiation therapy, chemotherapy, biological therapy, cryotherapy or hyperthermia.

The Examiner argued that because Cheng et al. disclosed that the expression of a wild-type p53 gene suppressed the growth of tumor cells *in vivo*; Srivastava disclosed vectors for gene

therapy; and Moossa et al. described radiation therapy, chemotherapy and other treatment methods; it would have been obvious to anyone of ordinary skill in the art to deliver a wild-type p53 gene to a cancer patient along with routine cancer therapies. However, none of these references described or suggested combining the two steps of this invention to increase the therapeutic effect of a cancer therapy.

Where one element of the claimed invention is found in one reference, and another element of the claimed invention is found in another reference, the teachings of the two references can be combined **only if** there is some suggestion or incentive to do so. In re Fine, 5 U.S.P.Q.2d 1596, 1599 (Fed. Cir. 1988). In addition, the motivation or suggestion for combining the teaching must be other than the knowledge learned from the disclosure of the applicant. In re Laskowski, 10 U.S.P.Q.2d 1397, 1398 (Fed. Cir. 1989). In this case, no suggestion or motivation existed in the prior art or was given in the references cited by the Examiner.

Although Chen et al. described that a wild-type p53 gene reduced tumor cells' ability to form colonies in soft agar

and tumors in nude mice, they did not describe or suggest using a wild-type p53 gene to make the tumor cells more sensitive to chemotherapy or radiation. Wu et al., Eppstein et al., and Nabel et al. described methods for delivering genes or proteins to cells but did not describe delivering a wild-type p53 gene into tumor cells to sensitize them to cancer therapies. Itoh et al. described cloning the Fas antigen and an antibody against the Fas antigen but did not describe delivering a wild-type Fas gene into tumor cells to sensitize them to cancer therapies.

The references cited in the Final Office Action each described a part of the claimed process but they did not describe the whole process or suggest combining the parts to make the whole process. The only way the disclosures of Cheng et al. and other references cited by the Examiner can be read to result in the above statement is with benefit of Applicant's disclosure.

Such use of Applicant's disclosure would be improper in an obviousness analysis. Selective hindsight cannot be used to evaluate obviousness. There must be a reason or suggestion in the prior art for selecting the procedure used, other than the knowledge learned from the applicant's disclosure. In re Dow

Chem. Co., 5 U.S.P.Q.2d 1529, 1532 (Fed. Cir. 1988).

C. The motive of the prior art references is different from that of the claimed invention

The Examiner argued in the obviousness rejection that Cheng et al. had suppressed the growth of leukemia cells (T-ALL) by introducing a wild-type p53 gene into the tumor cells. Therefore, the motive of Cheng et al. (and Chen et al.) is to use the wild-type p53 gene to reduce the growth rate of tumor cells. However, the tumor suppression effect of a wild-type p53 gene is different from the therapy sensitization effect of a wild-type p53 gene. Neither Cheng et al. or Chen et al. suggested using the wild-type p53 gene to sensitize tumor cells to cancer therapies.

That the wild-type p53 gene is a tumor suppressor, as reported in Cheng et al. and Chen et al., would not lead one skilled in the art to conclude that the wild-type p53 gene would increase the therapeutic effect of a cancer therapy. On the contrary, the growth suppressive effect of the wild-type p53 gene documented in Cheng et al. and Chen et al. would lead one skilled in the art to expect it to render tumor cells more resistant to

conventional chemotherapy and radiotherapy because chemotherapy and radiotherapy preferentially kill or suppress fast growing cells. In that regard, Cheng et al. and Chen et al. teach away from the invention claimed in this application.

Conventional chemotherapeutic and radiation regimens employed for the treatment of cancer are known to work by killing or suppressing cells undergoing rapid growth. Chemotherapeutic drugs and radiation are known to interfere with the mitotic or cell cycle process required for cell growth and division. It is known in the prior art that nondividing cells and slow-growing cells tend to be less susceptible to chemotherapy and radiation than fast-growing cancer cells. By this rationale, the expression of wild-type p53 gene in tumor cells would be expected to reduce, rather than increase, the sensitivity of the tumor cells to chemotherapy and radiation because wild-type p53 gene suppresses tumor cell growth.

It is improper to combine references where the references teach away from their combination. In re Grasselli, 218 U.S.P.Q. 769, 779 (Fed. Cir. 1983).

D. The claimed invention provides an unexpected result

Unexpected or surprising results achieved by the claimed invention may be strong support for nonobviousness. Lindemann Maschinenfabrik v. American Hoist & Derrick Co., 221 U.S.P.Q. 481, 488 (Fed. Cir. 1984). In this invention, the unexpected result of using a wild-type p53 gene to increase the therapeutic effect of chemotherapy and radiation therapy on tumor cells is shown in Figures 1 and 2, and Examples 4 and 5 of the specification.

Figure 1 and Example 4 show that tumor cells transduced with a wild-type p53 gene are more sensitive to cisplatin treatment than tumor cells lacking any wild-type p53 gene. Figure 2 and Example 5 show that tumor cells transduced with a wild-type p53 gene are more sensitive to radiation therapy than tumor cells lacking any wild-type p53 gene.

A prior art reference, Vogelstein et al., Cell 70: 523-526, (1992) (a copy is enclosed herein), stated on page 526 that "p53 mutations may therefore constitute one of the few oncogenic alterations that **increase** rather than decrease the sensitivity of cells to antitumor agents."

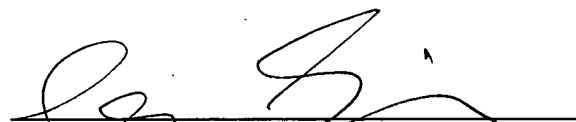
Contrary to the conventional wisdom and the teachings of prior art such as Vogelstein et al., Applicant found that the wild-type p53 gene increases the sensitivity of tumor cells to cancer therapies. This surprising discovery and its application as embodied in claims 1, 2, 4-10 and 23 were unexpected and not obvious from the prior art.

CONCLUSION

In view of the above discussion, Applicant submits that claims 1, 2, 4-20 and 23 are allowable. Applicant respectfully requests that they be allowed and passed to issue.

Respectfully submitted,

LYON & LYON



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APPENDIX

Claims

1. A method of increasing the therapeutic effect of a cancer therapy, comprising the steps of:

delivering a wild-type p53 gene to a tumor cell which is deficient in its wild-type p53 gene, effecting the expression of said wild-type p53 gene in said tumor cell, and

subjecting said tumor cell to said cancer therapy.

2. A method of increasing the therapeutic effect of a cancer therapy, comprising the steps of:

delivering a wild-type p53 protein to a tumor cell which is deficient in its wild-type p53 gene, and

subjecting said tumor cell to said cancer therapy.

4. The method of claim 1 wherein said cancer therapy is radiation therapy.

5. The method of claim 1 wherein said cancer therapy is chemotherapy.

6. The method of claim 1, wherein said cancer therapy is immunotherapy.

7. The method of claim 1, wherein said cancer therapy is cryotherapy.

8. The method of claim 1, wherein said cancer therapy is hyperthermia.

9. The method of claim 1 wherein said tumor cell is selected from the group consisting of leukemia cell, lymphoma tumor cell, ovarian carcinoma cell, osteogenic sarcoma cell, lung carcinoma cell, colorectal carcinoma cell, hepatocellular carcinoma cell, glioblastoma cell, prostate cancer cell, breast cancer cell, bladder cancer cell, kidney cancer cell, pancreatic cancer cell, gastric cancer cell, esophageal cancer cell, anal cancer cell, biliary cancer cell, and urogenital cancer cell.

10. The method of claim 1, wherein said wild-type p53 gene is in a vector.

11. The method of claim 10, wherein said vector is selected from the group consisting of adenovirus vector, retroviral vector, adeno-associated virus vector, herpes virus vector, vaccinia virus vector and papilloma virus vector.

12. The method of claim 1, wherein said wild-type p53 gene is coupled to a virus capsid or particle.

13. The method of claim 12, wherein said wild-type p53 gene is coupled to said capsid or particle through a polylysine bridge.

14. The method of claim 1, wherein said wild-type p53 gene is encapsulated in a liposome.

15. The method of claim 1, wherein said wild-type p53 gene is conjugated to a ligand.

16. The method of claim 15, wherein said ligand is an asialoglycoprotein.

17. The method of claim 1, wherein said wild-type p53 gene is introduced to said tumor cell by direct injection.

18. The method of claim 1, wherein said wild-type p53 gene is introduced to said tumor cell by intra-arterial infusion.

19. The method of claim 1, wherein said wild-type p53 gene is introduced to said tumor cell by intracavitary infusion.

20. The method of claim 1, wherein said wild-type p53 gene is introduced to said tumor cell by intravenous infusion.

23. The method of claim 1, wherein said wild-type p53 gene is introduced to said tumor cell in aerosolized preparation.